REMARKS

Applicants have received and reviewed an Office Action dated June 6, 2005. Applicants request entry of the amendment and response and reconsideration of the rejection of the claims.

Claims 1, 67 and 74 have been amended. The amendments are supported throughout the specification, including at page 3, lines 28-35; page 9, lines 15-29; page 13, line 18 to page 14, line 11. (page numbers and line numbers refer to specification as originally filed)

Claims 81-90 are new. Applicants submit that the newly presented claims are supported throughout the specification, including at page 3, lines 19-27; page 13, line 18 to page 14, line 11; page 9, lines 15-29; page 22, lines 5-15; page 24, line 33 to page 25, line 10; and page 27, line 34 to page 28, line 2.

Petition for Extension of Time

It is noted that a one-month petition for extension of time is necessary to provide for the timeliness of the response. A request for such an extension is made extending the time for response from September 6, 2005 to October 6, 2005.

Information Disclosure Statement

Applicants acknowledge the Examiner's consideration and return of the Information Disclosure Statement filed March 17, 2005.

Claims

35 U.S.C. §112, ¶1, Written Description

Claims 1, 3, 4, 8-10, 67-69, 71-76, and 78-80 were rejected under 35 U.S.C. §112, ¶1, for alleged lack of written description. We understand that the Examiner has several bases for this rejection as follows: 1) the Examiner contends that one of skill in the art could not readily recognize and envision tumor cells characterized by aberrant Wnt signaling, and 2) the Examiner contends that the specification does not describe the structural and functional variants of Stra6 protein. Applicants respectfully traverse.

The written description requirement is satisfied when Applicants' specification conveys with reasonable clarity to those skilled in the art, that as of the filing date sought, he or she was

in possession of the invention. Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, 1116 (Fed. Cir. 1991).

"The description needed to meet the requirement varies with the nature and scope of the invention at issue, and with the scientific and tcchnologic knowledge already in existence. The law must be applied to each invention that enters the patent process, for each patented advance is novel in relation to the state of science. Since the law is applied to each invention in view of the state of relevant knowledge, its application will vary with differences in the state of knowledge in the field and differences in the predictability of the science." *Capon v. Eshar*, 2005 U.S. App. LEXIS 16865 (Fed Cir. 2005).

Moreover, as noted in the Guidelines for Examination of Patent Applications Under 35 U.S.C. § 112, ¶1, "Written Description" Requirement ("the guidelines"), there is a "strong presumption" that an adequate written description of the claimed invention is present when the application is filed, 66(4) Fed Reg. 1099, 1105 (2001); see also, In re Wertheim, 191 USPQ 90,97 (CCPA 1976). The guidelines further state that "The examiner has the initial burden of presenting by a preponderance of evidence why a person skilled in the art would not recognize in an applicant's disclosure a description of the invention defined by the claims." 66(4) Fed. Reg. at 1107; 191 USPQ at 97, (emphasis added).

With respect to the Examiner's contention that the specification does not adequately describe tumor cells characterized by aberrant Wnt signaling, Applicants submit the specification as filed provides adequate written description.

Contrary to the assertion of the Examiner, description of every tumor cell characterized by aberrant Wnt signaling is not a requirement for having adequate written description. Applicants need only supply sufficient description to show possession of the invention. In the present specification, Applicants provide both general description and demonstrate multiple examples of tumor cells characterized by aberrant Wnt signaling. Extensive guidance is provided throughout the specification, including in Example 13, beginning at page 66, and Example 15, beginning at page 79, demonstrating enhanced expression of Stra6 in tumor cells by Wnt-1 in combination with retinoids as well as in tumor cells having alterations in APC and β catenin.

Furthermore, the specification provides teachings to identify aberrant signaling of the Wnt pathway in tumor cells. The members and relationships of proteins/molecules in the Wnt

signaling pathway are described at pages 13-14, thereby providing further guidance to recognize tumor cells characterized by aberrant Wnt signaling. Additionally, multiple examples of tumor cells or tissues that have been found to have altered expression of members of the Wnt signaling pathway have been described. Human cancers that harbor genetic defects in the Wnt-1 pathway, such as the majority of colorectal tumors which contain mutations in the genes coding for either the APC tumor suppressor or β-catenin, can be targeted for immunotherapy through retinoid/Wnt induced overexpression of Stra6 on the tumor cell surface. Selective enhancement of protein expression (e.g., Stra6) of cancer cells relative to normal cells generally improves the therapeutic index for immunotherapeutics directed against that antigen. See specification at page 70, line 22 through page 71, line 37.

The knowledge in the art regarding the Wnt signaling pathway and the ability to identify aberrant Wnt signaling, in combination with the multiple species of tumor cells characterized by aberrant Wnt signaling that are described in the specification, provide written description for the genus of tumor cells characterized by aberrant Wnt signaling.

Applicants note that claim 67 is directed to a method for the synergistic enhancement of expression of a Stra6 protein in a tumor cell comprising treating said tumor cell with an effective amount of a retinoid to synergistically enhance expression of a Stra 6 protein having at least 95% sequence identity to a polypeptide comprising an amino acid sequence of SEQ ID NO:2, wherein said tumor cell is characterized by expression of Wnt-1. Claim 76 is directed to a method for selective enhancement of the expression of a Stra6 protein in a tumor cell comprising treating said tumor cell with an effective amount of a retinoid to selectively enhance expression of a Stra6 protein having least 95% sequence identity to a polypeptide comprising SEQ ID NO:2, wherein the tumor cell is characterized by aberrant signaling of a member of the Wnt pathway selected from the group consisting of Wnt gene family, APC, catenin, frizzled receptors, dishevelled protein, glycogen synthase kinase-3β, transcription factor TCF/LEF-1, nodal related 3 gene, Xnr3, the homeobox genes, engrailed, goosecoid, twin (Xtwn), siamois, c-myc and the WISP genes.

Applicants submit that they have described these members of the Wnt pathway and described tumor cells that have aberrant signaling associated with members of the pathway. See, for example, pages 13-14 in the specification. In addition, Applicants submit that they have demonstrated that tumor cells with alterations in different members of the pathway have

selectively enhanced expression of Stra6. For example, cells that express Wnt-1 have enhanced expression of Stra6, as well as cells that have alterations in APC or B catenin. See the specification at page 69, lines 3-31 and at page 70, line 21 to page 71, line 4. Moreover, Applicants submit that their claims are directed to a method of treating tumor cells having an alteration in a member of the pathway and not to the altered members of the pathway themselves. In view of the knowledge of those of skill in the art with respect to the members of the pathway, Applicants do not need to provide all sequences or variations of the members of the pathway. See *Capon v. Eshar*, 2005 U.S. App. LEXIS 16865 (Fed Cir. 2005). Applicants need only describe tumor cells that have aberrant Wnt signaling and Applicants submit that they have done so.

Applicants submit that the specification as filed adequately describes tumor cells characterized by aberrant Wnt signaling for at least the reasons discussed above. Applicants also would like to respond specifically to some of the statements made by the Examiner in the Office Action.

On page 4, of the Office Action, Applicants disagree with the Examiner's characterization of the Applicants' specification as providing only a few known members of the pathway. Applicants submit that the specification describes more than a few members of the pathway at pages 13-14. Applicants have described many genes that have been identified in the Wnt signaling pathway. Applicants submit this extensive description is sufficient to support written description of a tumor cell characterized by aberrant Wnt signaling.

At the top of page 5, the Office Action asserts that "In this instance, there is no language that adequately describes at least a substantial number of the members of the genus of proteins involved in a Wnt signaling pathway that are aberrantly expressed in tumor cells that may be treated with an effective amount of a retinoid to achieve the claimed effect." Applicants disagree. Extensive description is provided in the specification for members of the Wnt signaling pathway, as well as numerous examples of tumor cells having aberrant Wnt signaling that may be treated according to the claims. See citations provided above.

The second and third paragraphs on page 5 of the Office Action state that the claimed method depends on tumor cells characterized by aberrant Wnt signaling and then assert that "written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it." Applicants disagree that a "mere statement" has

been provided to support tumor cells characterized by aberrant Wnt signaling and respectfully refer to the description at pages 12-13 and experimental data provided in the specification on pages 61 thru 80.

On page 6, the Office Action asserts "In this instance, factual evidence of an actual reduction to practice has not been disclosed by Applicant in the specification." Applicants disagree. Please see experimental data provided in the specification on pages 61 thru 80, demonstrating selective enhancement of Stra6 expression in tumor cells characterized by aberrant Wnt signaling.

Based on the foregoing, Applicants request withdrawal of the 35 U.S.C. § 112, first paragraph, rejection on this basis.

The Examiner also rejected the claims contending that the written description does not support the genus of Stra6 variants. While Applicants do not agree with the rejection, in order to expedite prosecution, Applicants have amended the claims to refer to a Stra6 polypeptide having at least 95% sequence identity to a polypeptide comprising an amino acid sequence of SEQ ID NO:2. Applicants submit that the specification describes such variants at page 9, lines 12-19. Applicants have further characterized the Stra6 protein by providing identification of transmembrane, glycosylation sites, and n-myristoylation sites. (See Figure 2.) Applicants have also described and shown a variant of a Stra6 polypeptide comprising an amino acid sequence of SEQ ID NO:5. Therefore, Applicants respectfully request withdrawal of the 35 U.S.C. § 112, first paragraph, rejection on this basis.

35 U.S.C. §112, ¶2, Indefiniteness

Applicants acknowledge the Examiner's consideration and withdrawal of previous rejections under 35 U.S.C. §112, ¶2.

35 U.S.C §102(a)

Claims 1, 3, 4, 8-10, 67-69, 71-76, and 78-80 are rejected under 35 U.S.C. § 102(a) as being anticipated by Chu et al. (*J. Nutr.* 129: 1846-1854, 1999) (hereinafter Chu), as evidenced by Pennica et al. (*Proc. Natl. Acad. Sci. USA* 95: 14717-14722, 1998) and Szeto et al., (*Cancer Res.* 61: 4197-4205, 2001) (hereinafter Szeto). The Examiner has several bases for the rejection. As we understand it, the Examiner contends that 1) the claims do not recite that selective

enhancement is achieved and the Examiner further contends Szeto et al. provides evidence that the process disclosed by the prior art did result in selective enhancement of Stra6 in tumor cells; 2) the Examiner contends that the claims do not require synergistic enhancement of expression of Stra6; 3) the Examiner contends that Chu et al. teaches an amount of a retinoid effective to induce expression of Gpx2; and 4) the Examiner contends that it is proper to cite post filing date references. Applicants respectfully traverse.

Under 35 U.S.C. §102, "A claim is anticipated only if each and every element as set forth in the claim is found either expressly or inherently described in a single prior art references." Verdegaal Bros. v. Union Oil of California, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). The fact that a *certain* result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic. MPEP § 2112. The prior art characteristic must be established as a certainty, probabilities are not sufficient. In re Oelrich, 666 F.2d 578, 581 (CCPA 1981). The Examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teaching of the prior art. Ex parte Levy, 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Inter. 1990).

Claims 1, 3, 4, and 8-10 are directed to methods for selectively enhancing the expression of a Stra6 protein in a tumor cell comprising treating said tumor cell with an effective amount of a retinoid to selectively enhance expression of a Stra6 protein having at least 95% sequence identity to a polypeptide comprising an amino acid sequence of SEQ ID NO:2, wherein the tumor cell is characterized by aberrant Wnt signaling. Claims 67-69 and 71-73 are directed to synergistic enhancement of Stra6 protein in a tumor cell comprising treating said tumor cell with an effective amount of a retinoid, to synergistically enhance expression of a Stra6 protein having at least 95% sequence identity to a polypeptide comprising an amino acid sequence of SEQ ID NO:2, wherein said tumor cell is characterized by expression of Wnt-1. Claims 74-76, and 78-80 are directed to a method for selective enhancement of Stra6 protein in a tumor cell, wherein the tumor cell is characterized by aberrant signaling of a member of the Wnt pathway selected from the group consisting of Wnt family, APC, catenin, frizzled receptors, dishevelled protein, glycogen synthase kinase-3β, transcription factor TCF/LEF-1, nodal related 3 gene, Xnr3, the homeobox genes, engrailed, goosecoid, twin (Xtwn), siamois, c-myc and the WISP genes comprising treating said tumor cell with an effective amount of a retinoid to selectively enhance

expression of a Stra6 protein having at least 95% sequence identity to SEQ ID NO:2.

The Chu et al. reference does not explicitly or inherently disclose all of the elements or limitations of Applicant's claims. The Chu et al. reference does not disclose selective enhancement of Stra6 proteins in a tumor cell characterized by aberrant Wnt signaling, nor does Chu et al. disclose the synergistic enhancement of expression by a combination of Wnt pathway and said retinoid. Chu et al. also does not disclose or discuss alterations to the members of the Wnt signaling pathway. The Examiner admits that there is no discussion in Chu et al. of Stra6 or other proteins, or of tumor cells characterized by altered Wnt signaling or synergistic enhancement of the expression of Stra6 by the combination of aberrant Wnt signaling and retinoid.

The Examiner asserts that Pennica establishes that breast and colon cells are characterized by altered Wnt signaling and that Chu et al. teaches treating colon and breast cancer cells with an effective amount of retinoic acid to affect expression of genes in cells. However, as discussed previously, the only cells that are common between Pennica and Chu et al. are HT-29 cells. The Chu et al. reference explicitly states that the expression of Gpx2 mRNA in MDA MB-231 and HT-29 was not significant (see page 1851, col. 1 of Chu et al.). Moreover, the Chu et al. reference states they did not detect Gpx2 mRNA in HUTU80 (human duodenum cancer cell lines), IEC-6 and IEC-18 cell lines (small intestine cell line) with and without treatment. (See page 1852, col. 2, last paragraph). One of the cell lines did have functional RAR and the authors concluded it was not clear why the Gpx2 gene could not be induced in the cells.(See the last paragraph on page 1852 to the top of page 1853)

Secondly, the Examiner has failed to establish that the missing descriptive matter is necessarily present in the alleged anticipatory reference and to provide a basis in fact or technical reasoning to reasonably support the determination that the alleged inherent characteristic necessarily flows from the teachings of the applied prior art. The possibility that missing descriptive matter may be present in the prior art is not sufficient. Applicants submit that the majority of breast and colon cell lines of Chu et al., including HT29, did not show an increase in expression of Gpx2. This fact indicates that the missing descriptive matter is not necessarily present in the anticipatory reference and does not establish a sound basis in fact or technical reasoning that the allegedly inherent characteristic necessarily flows from the prior art. Moreover, expression of Gpx2 would not teach one of skill in the art that expression of Stra6

would be enhanced or synergistically enhanced. Neither Pennica nor Chu et al. discuss expression of Stra6 in any type of cell.

Moreover, Applicants submit that the Examiner is using a post filing date reference, Szeto et al., which includes some of Applicant's own work, to inappropriately supply claim elements missing from the prior art rather than to confirm the contents of the prior art. See Teleflex v. Ficosa North America, 63 USPQ2d 1374,1388 (Fed. Cir. 2002) As discussed above, the Examiner has not established that all of the elements of the claimed invention are necessarily present in the prior art reference. For example, neither Pennica nor Chu disclose that tumor cells characterized by aberrant Wnt signaling can be treated with a retinoid in order to selectively and/or synergistically enhance expression of Stra6. Applicants respectfully submit the Examiner is using Szeto et al in hindsight reconstruction to supply those claim elements missing from the primary reference.

Applicants respectfully request withdrawal of the 35 U.S.C. § 102(b) rejection of claims 1, 3, 4, 8-10, 67-69, 71-76, and 78-80 based on Chu et al. The Examiner has failed to establish that all of the elements of the claims are found in a single prior art reference. The secondary references cited by the Examiner do not show the missing descriptive matter is necessarily present in Chu et al. Thus, Applicants respectfully request withdrawal of this rejection.

New Grounds of Rejection under 35 U.S.C. §102(a)

Claims 1, 3, 4, 8-10, 67-69, 71-76, and 78-80 are rejected under 35 U.S.C. §102(a) as anticipated by van der Leede et al. (Mol Carcinog. (1993) 8(2):112-122), as evidenced by Szeto (of record).

The van der Leede reference does not explicitly or inherently disclose all of the elements or limitations of Applicant's claims. The van der Leede reference does not disclose selective enhancement of Stra6 proteins in a tumor cell characterized by aberrant Wnt signaling, nor does van der Leede disclose the synergistic enhancement of expression by a combination of Wnt pathway and a retinoid. Van der Leede also does not disclose or discuss alterations to the members of the Wnt signaling pathway. Van der Leede describes that some tumor cell lines are resistant to retinoic acid, including HT116. Further, expression of retinoic acid receptors was not induced or correlated with retinoic acid exposure or resistance to retinoic acid. (See page 119.) The Examiner admits that there is no discussion in van der Leede of expression of Stra6, or cells

characterized by aberrant Wnt signaling that when treated with retinoid causes selective enhancement of the expression of Stra6 by the combination of Wnt and retinoid.

Applicants respectfully request withdrawal of the 35 U.S.C. § 102(b) rejection of claims 1, 3, 4, 8-10, 67-69, 71-76, and 78-80 based on van der Leede. The Examiner has failed to establish that the all of the elements of the claims are found in a single prior art reference. The secondary reference cited by the Examiner does not confirm that all of the claim limitations are necessarily present but rather impermissibly supplies claim elements missing from the primary reference. Thus, Applicants respectfully request withdrawal of this rejection.

Claims 1, 3, 4, 8-10, 67-69, 71-76, and 78-80 are rejected under 35 U.S.C. §102(a) s anticipated by Keogh et al. (Cancer Biochem Biophys. (1993) 13(3):209-220), as evidenced by Szeto et al. (of record).

The Keogh reference does not explicitly or inherently disclose all of the elements or limitations of Applicant's claims. The Keogh reference does not disclose selective enhancement of Stra6 proteins in a tumor cell characterized by aberrant Wnt signaling, nor does Keogh disclose the synergistic enhancement of expression by a combination of Wnt pathway and said retinoid. Keogh also does not disclose or discuss alterations to the members of the Wnt signaling pathway. Keogh describes lack of any increase in the transglutaminase when WiDr cells and Sw480 cells were exposed to retinoic acid alone. (See page 216 and Figures 6 and 7.) The Examiner admits that there is no discussion in Keogh of Stra6 expression, or cells characterized by aberrant Wnt signaling that when treated with retinoid causes selective enhancement of the expression of Stra6 by the combination of Wnt and retinoid.

Applicants respectfully request withdrawal of the 35 U.S.C. § 102(b) rejection of claims 1, 3, 4, 8-10, 67-69, 71-76, and 78-80 based on Keogh. The Examiner has failed to establish that the all of the elements of the claims are found in a single prior art reference. The secondary reference cited by the Examiner does not confirm that all of the claim limitations are necessarily present but rather impermissibly supplies claim elements missing from the primary reference. Thus, Applicants respectfully request withdrawal of this rejection.

Interview

Applicants will contact the Examiner to schedule an interview.

Summary

In view of the above amendments and remarks, Applicants respectfully requests a Notice of Allowance. If the Examiner believes a telephone conference would advance the prosecution of this application, the Examiner is invited to telephone the undersigned at the below-listed telephone number.

Respectfully submitted,
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Date: October 6, 2005

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